IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo, et al. : Examiner: B. Fubara

SERIAL NO.: 09/742,785 : Art Unit: 1615

FILED: December 20, 2000 :

FOR: Pharmaceutical Compositions
Providing Enhanced Drug Concentrations

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT AND RESPONSE

This paper is responsive to the Final Office Action mailed on March 13, 2006 and to the Advisory Action mailed on February 1, 2007. A current claim summary is appended as part of this response, starting on its own separate sheet.

Remarks

References herein to Applicants' specification are to bracketed paragraph numbers in the application published as US 2002/0006443 A1.

As a preliminary matter, it is noted that Applicants filed a Notice of Appeal in this application on September 13, 2006. Applicants' opening brief was accordingly due, without extension, on or before November 13, 2006, which time has been extended to March 13, 2007. In lieu of filing an opening brief, Applicants' have filed a Request For Continued Examination (RCE) and an Amendment responsive to the Office Action dated March 13, 2006 and the Advisory Action dated February 1, 2007.

As a preliminary matter, attention is directed to the Petition For Extension of Time (four months) and to the Request For Continued Examination (RCE) enclosed herewith.

The status of the claims can be summarized as follows:

Claims canceled: 16-17, 45-46, 73-74, 93-94, 103, 113-114, 123, 133-134, 146-155, and 162-163

Claims withdrawn:	3-11, 19-24, 32-40, 48-53, 60-68, 76-81, 88-91, 96-101, 108-111, 116-121, 128-131, and 136-141
Claims pending:	1-15, 18-44, 47-72, 75-92, 95-102, 104-112, 115-122, 124-132, and 135-145 and 156-161
Claims allowed:	None
Claims rejected:	1, 2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, 142-145 and 156-161

Each of independent claims 1, 30, 58, 86, 106, and 126 has been amended by changing the word "drug" to "solubility improved form" in the next-to-last line. The amendment is formal and has been made to clarify that the term "drug" in the physical mixture means the solubility improved form thereof rather than the free form or a non-solubility improved form. Support for the amendment is at page 11, lines 2-8. Entry of the amendment is accordingly respectfully requested.

Claims 146-155 and 162-163 have been canceled in order to reduce the issues under consideration.

Argument

Applicants' arguments against each ground of rejection are offered below. As a preliminary matter, Applicants respectfully submit it would be useful to offer a brief description of the invention and the technical advances it offers.

The invention relates to physical mixtures that increase the concentration of low solubility drugs, i.e., those having an aqueous solubility less than about 1 mg/mL. The compositions generally comprise a physical mixture of a solubility-improved form of a low-solubility drug and a concentration-enhancing polymer which is believed to act by inhibiting precipitation, the particular concentration-enhancing polymers being specified in each of the independent claims on appeal. The solubility-improved form of the drug, when the composition is dissolved in the use environment, provides an initial concentration of drug that exceeds the equilibrium concentration of drug in its sparingly soluble (usually free) form, while the concentration-enhancing polymer retards the rate at which the initially enhanced drug concentration falls back to the equilibrium concentration. Thus the concentration of a sparingly soluble drug can be increased (due to the solubility-improved form) and the concentration

enhancement can be prolonged (due to the polymer, which acts to inhibit precipitation) without the need for forming a molecular dispersion prior to administration. The difference between a molecular dispersion and a physical mixture is disclosed at paragraph [0034] and [0037]. Many different types of solubility-improved drug forms are also disclosed in paragraph [0024].

Applicants' arguments against each of the grounds of rejection follow.

1. Claims 1, 2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135 and 142-145 are not anticipated under 35 U.S.C. 102(b) by Miyajima et al. (US 4,983,593).

As a preliminary matter it is noted that Miyajima relates generally to compositions of a single drug, designated therein as "NZ-105" and HPMCAS, one of the concentration-enhancing polymers named in Applicants' claims. NZ-105 is a hydrochloride ethanolate form of the molecule efonidipine. See the Okabe et al journal article discussed in greater detail below. NZ-105 is also crystalline. See The Merck Index, Twelfth Edition, Published by Merck Research Laboratories, Division of Merck & Co., Inc., Whitehouse Station, NJ, page 595, Entry 3566, copy included herewith.

The law is well settled regarding the issue of anticipation. To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. Karsten Mfg. Corp. v. Cleveland Golf Co., 242 F.3d 1376, 1383, 58 USPQ2d 1286, 1291 (Fed. Cir. 2001). See also C.R. Bard, Inc. v. M3 Systems, Inc., 157 F.3d 1340, 1349 (Fed. Cir. 1998). Miyajima does not anticipate because (1) it does not disclose a solubility-improved form of NZ-105 within the scope of Applicants' claims and (2) it also fails to disclose a composition of HPMCAS and NZ-105 that is a physical mixture, as Applicants' claims specifically require.

Relevant to reason (1) Applicants' claims specifically exclude crystalline hydrochloride salts. More specifically, Applicants' claims state that when the drug is basic, the solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form. NZ-105 is a crystalline hydrochloride salt and, as such, has been excluded from the claims. Salts are defined as substances produced from the reaction between acids, in this case HCl, and bases, in this case the NZ-105 base molecule efonidipine. Grant & Hackh's Chemical Dictionary, Fifth Edition, published by McGraw-Hill, page 516 (copy previously supplied). The fact that a crystalline

hydrochloride salt also contains a solvent molecule is irrelevant. It is still a crystalline hydrochloride salt. NZ-105 is, therefore, outside the scope of Applicants' claims.

In support of the contention that NZ-105 is a crystalline hydrochloride salt, Applicants note that NZ-105 is recognized as a hydrochloride salt by those skilled in the art. Applicants enclose a copy of "Dissolution Behavior of Efonidipine Hydrochloride" by Okabe et al., Pharmaceutical Sciences, 1995, Vol. 1, Pp 255-258 (copy previously supplied) in which, in the left hand column of page 255 (under "Materials and Methods") the following statement is made:

> The hydrochloride (Fig. 1) is a salt form made by adding hydrochloride and ethanol to efonidipine.

The Examiner's attention is also respectfully directed to Figure 1 in which the structure for the ethanolate of efonidipine hydrochloride is illustrated above the legend "Fig. 1. Structural formula of efonidipine hydrochloride".

The Examiner's comment (OA of 3/15/06) in Paragraph 2 that

> Secondly, the proviso does not exclude NZ-105 as drug in a pharmaceutically acceptable form. There is no factual evidence that the NZ-105 would not have at least 2 fold the solubility of the more soluble of the crystalline hydrochloride salt.

misses the point. It is respectfully submitted that no testing or other "factual evidence" is required because there is no issue relating to whether NZ-105 was effectively excluded. All of Applicants' independent claims require the solubility-improved form to have "an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form". That language effectively excludes <u>both</u> species, i.e., both the crystalline hydrochloride salt and the crystalline free base. If NZ-105 is more soluble than efonipine free base (which it is factually), it is excluded by virtue of not having the requisite solubility. Even if NZ-105 were less soluble than efonidipine free base, it is still excluded because its solubility would be too low to meet the claim requirement of having "...at least 2-fold the solubility of the <u>more soluble</u> of the crystalline hydrochloride salt and the crystalline free base. Neither form can be within the scope of Applicants' claims. Thus, regardless of the solubility of NZ-105, Applicants have excluded all crystalline drug hydrochlorides, including NZ-105, from the claims.

Further, Miyajima does not anticipate because Miyajima does not disclose a composition of HPMCAS and NZ-105 that is a simple physical mixture. Miyajima prepares his compositions by dissolving NZ-105 and HPMCAS in an organic solvent and removing the solvent by

evaporation. Miyajima at column 2, lines 37-40. Miyajima's process is thus a solvent based process which produces solvent based compositions and which would not produce a simple physical mixture. The differences are well explained in Applicants' specification in Paragraph [0029], the pertinent part being reproduced as follows:

> In the compositions of the present invention, as disclosed above, the drug and polymer each retain their individual respective physical properties, such as melting point and/or glass-transition temperature. Thus, solid compositions made by dissolving a drug plus the concentration-enhancing polymer in a solvent followed by drying from the solvent, or by co-grinding, or by extruding with heating, or by precipitation by mixing a solution of the polymer and a solution of the drug such that a dispersion of polymer and drug precipitates, or by other methods such that a molecular dispersion of drug and concentration-enhancing polymer is formed do not form a part of this invention.

Miyajima's solvent processing method would not produce a physical composition as defined by Applicants, i.e., one in which the individual components retain the same individual physical properties that they exhibit in bulk, as defined in paragraph [0031].

Because Miyajima does not disclose a composition that is a physical mixture, and in fact discloses only solvent based compositions, it cannot anticipate.

The Examiner's comments in the advisory action relating to wet granulation are noted. Wet granulation does not dissolve the drug and the solubility improved form to create a solution as in Miyajima, however, and the individual components still retain their bulk properties.

For all of the above reasons, it is submitted that Applicants cannot be anticipated by Miyajima, and it is respectfully requested that the rejection be withdrawn.

2. Claims 1, 2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75 and 82-85 are not anticipated under 35 U.S.C. 102(b) by Dunn (US 4,461,759)

Dunn relates to a constant order release, solid oral dosage formulation of the cardiovascular drug verapamil or a pharmaceutically acceptable salt thereof, verapamil hydrochloride being the only such salt disclosed. Dunn does not anticipate because, *inter alia*, verapamil and verapamil hydrochloride, the only drug species Dunn specifically discloses, are not solubility-improved forms within the scope of Applicants' claims.

Both verapamil and verapamil hydrochloride are outside the scope of Applicants' claims by virtue of the fact that neither has "an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form". The language just quoted excludes the more soluble drug form whether it is the crystalline

hydrochloride salt or the free base, it being noted that verapamil hydrochloride is crystalline. See The Merck Index, 13th edition, page 1696, entry 10083 (copy enclosed). The remaining form is also excluded by virtue of being the less soluble of the two forms. Thus both verapamil and verapamil hydrochloride, i.e., the hydrochloride salt and the free base, are unequivocally excluded.

As noted above, verapamil and verapamil hydrochloride are the only drug forms disclosed in Dunn within the scope of the phrase "verapamil or a pharmaceutically acceptable salt thereof". No other verapamil species is disclosed. Dunn accordingly fails to disclose a solubility-improved form within the scope of Applicants' claims. Dunn discloses nothing else that would constitute a solubility-improved form physically mixed with any concentration-enhancing polymer required by Applicants' claims. Because the required element of a solubility improved form is missing from Dunn, and because an anticipatory reference must disclose all elements of an invention, Dunn does not anticipate Applicants' claims. Karsten Mfg. Corp. v. Cleveland Golf Co., supra.

It is accordingly respectfully submitted that the 35 U.S.C. 102(b) rejection over Dunn should be withdrawn.

3. Claims 1, 2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 125-127, 132, 135 and 142-145 are not anticipated under 35 U.S.C. 102(b) by Okada et al. (US 5,496,561).

Okada does not anticipate because it does not disclose a drug in a solubility-improved form physically mixed with a concentration-enhancing polymer within the scope of Applicants' claims.

Okada discloses a controlled release-rate pharmaceutical composition in which a drug-containing composition is coated with a membrane layer that contains a water insoluble high polymer and silicone. Okada, column 2, lines 2-5. Okada names cellulose acetate phthalate, one of the concentration-enhancing polymers named by Applicants, as one of the water-insoluble high polymers that can be used in the membrane layer of his pharmaceutical composition. Column 4, lines 11-13 and 22-23. In the Office Action of August 4, 2005, the Examiner contended that Okada's disclosure of CAP as a constituent in a membrane surrounding Okada's drug-containing core constituted a "physical mixture" within the scope of Applicants' claims.

> Although Okada does not disclose examples of composition that contains CAP, it is respectfully noted that, a prior art does not have to exemplify all the different embodiments. There is however a disclosure of CAP with a drug. Specifically, page 10, line 23 to page 11, line 12 of the instant specification and paragraph [0029] of the published application states that combination "as used herein means that the solubility-improved form and concentration-enhancing polymer may be in physical contact with each other or in close proximity but without the necessity of being physically mixed. For example, the solid composition may be in the form of a multi-layer tablet, as known in the art, wherein one or more layers comprises the solubility-improved form and one or more different layers comprises the concentration-enhancing polymer. Yet another example may constitute a coated tablet wherein either the solubility-improved form of the drug or the concentration-enhancing polymer or both may be present in the tablet core and the coating may comprise the solubility-improved form or the concentration-enhancing polymer or both. Alternatively, the combination can be in the form of a simple dry physical mixture wherein both the solubility-improved form and concentration-enhancing polymer are mixed in particulate form and wherein the particles of each, regardless of size, retain the same individual physical properties that they exhibit in bulk. Any conventional method used to mix the polymer and drug together such as physical mixing and dry or wet granulation, which does not substantially convert the drug and polymer to a molecular dispersion, maybe used." Thus, contrary applicants' assertion, coatings are not excluded by the combination or the physical mixing does not exclude coating. Maximum drug concentration (claim 1), which is the area under the curve (claim 30) is a property of the composition and in this case the composition is generic to a combination of drug and polymer (concentration-enhancing polymer). Examiner has not juxtaposed Okada on applicants' specification. Rather, the claims are directed to broad subject matter of drug combined with any of the polymers recited. [Pages 6-7 of the August 4, 2005 Office Action].

Applicants respectfully submit the Examiner is mistaken and misinterpreted the portion of Applicants' specification she relied on to make the rejection. The Examiner appeared to be arguing that Okada's disclosure of CAP being used in a membrane surrounding a core containing his drug constitutes a "physical mixture" within the scope of Applicants' claims. A threshold issue here is whether a physical mixture (in which a concentration enhancing polymer and a solubility-improved drug form are "mixed") can be equated with Okada's membrane-coated device (in which the drug is in a core surrounded by, but not physically mixed with, a membrane containing the polymer). That interpretation is contrary to what one skilled in the art understands a physical mixture to be, and contrary to Applicants' definition of a physical mixture. The portion of Applicants' text quoted by the Examiner, as set forth in the above quotation from the 8/04/05 Office Action, is directed to explaining the meaning of the term "combination", and disclosed, *inter alia*, that a physical mixture is one form of a "combination".

But, there is no basis in that text for concluding that "physical mixture" includes any embodiment in which a drug contained in a core is surrounded by a membrane containing, as a fixed and separate structural element, a polymeric membrane.

To the contrary, the very language cited by the Examiner from Applicants' specification supports that Okada discloses no embodiment in which a solubility-improved drug is physically mixed with one of Applicants' named concentration-enhancing polymers. Applicants' text at page 10, line 23 to page 11, line 12 defines what is meant by the broad term "combination". It explains that a physical mixture is an embodiment within the scope of "combination". The first clause quoted by the Examiner, namely

> [combination] "as used herein means that the solubility improved form and concentration-enhancing polymer may be in physical contact with each other or in close proximity **but without the necessity of being physically mixed**." [Emphasis supplied]

indicates that some embodiments which qualify as "combinations" are not physically mixed (hence they cannot be physical mixtures).

The second and third sentences of the quotation describe examples of "combinations":

> For example, the solid composition may be in the form of a multi-layer tablet, as known in the art, wherein one or more layers comprises the solubility-improved form and one or more different layers comprises the concentration-enhancing polymer. Yet another example may constitute a coated tablet wherein either the solubility-improved form of the drug or the concentration-enhancing polymer or both may be present in the tablet core and the coating may comprise the solubility-improved form or the concentration-enhancing polymer or both.

The fourth sentence of the quotation, by its use of the transition "Alternatively", signals that something different (i.e., a physical mixture) is about to be disclosed. The text then goes on to describe physical mixtures and how physical mixing can be achieved:

> Alternatively, the combination can be in the form of a simple dry physical mixture wherein both the solubility-improved form and concentration-enhancing polymer are mixed in particulate form and wherein the particles of each, regardless of size, retain the same individual physical properties that they exhibit in bulk. Any conventional method used to mix the polymer and drug together such as physical mixing and dry or wet granulation, which does not substantially convert the drug and polymer to a molecular dispersion, may be used.

There is nothing in the any of the above passages indicating that a drug in a core surrounded by a membrane constitutes a physical mixture. The full text of the quotation simply reviews different forms of a "combination".

Although Applicants offered the above explanation in their response to the 8/04/05 Office Action, the Examiner appeared to pursue the same line of rejection in the final Office Action of 3/13/06, stating in paragraph 7 that:

> The instant composition comprises a drug and concentration enhancing polymer, where the composition is a dispersion and does not exclude the composition of Okada because Okada does not describe the formation of covalent or ionic bond between the drug and the polymer, such a bond formation would not be a physical process. Also, there is no claim to a physical composition in the examined claims. [Emphasis supplied]

Applicants disagree and submit the rejection should be withdrawn on several grounds.

First, Applicants' composition is not a dispersion. Dispersions are specifically excluded from the claims.

Second, the Examiner appears to be contending that chemical bonds between the drug and polymer membrane in Okada would need to form in order to preclude Okada's drug/polymer membrane embodiment from qualifying as a physical mixture. Applicants respectfully disagree. It is well accepted that an applicant can define her own terms, i.e. she can be her own lexicographer. See Beachcombers, International, Inc. v. WildeWood Creative products, Inc., 31 USPQ2d 1653, at 1656 (Fed Cir 1994) where the court stated:

> As we have repeatedly said, a patentee can be his own lexicographer provided the patentee's definition, to the extent it differs from the conventional definition, is clearly set forth in the specification

Thus, as a threshold consideration Applicants were clearly permitted to define the phrase "physical mixture" as they wished. Thus, a physical mixture is as Applicants defined it in their specification. Applicants defined a physical mixture of a solubility-improved drug and polymer to be, *inter alia*, a composition of drug and polymer that has been physically mixed. That is, some form of mixing action is required to make a mixture. See the specification at paragraph [0029] where Applicants indicate that the individual components retain their bulk properties and that any conventional method may be used to mix the polymer and drug together. The dosage form disclosed in Okada, by contrast, is a structure, not a physical mixture. It comprises a polymeric membrane surrounding a central core containing drug, the membrane constituting a fixed element in the structure and in which no mixing of membrane components and core

components is involved. No embodiment is disclosed in Okada wherein a concentration enhancing polymer required by Applicants is physically mixed with a solubility-improved form of a drug.

Third, Applicants respectfully submit the Examiner was mistaken in her contention that "...there is no claim to a physical composition in the Examined claims". To the contrary, Applicants' claims specifically require that the drug and polymer are combined as a simple physical mixture.

Applicants further submit that Okada is legally insufficient to support the rejection. An anticipation rejection requires the presence in a single prior art reference of each and every element of the claimed invention, arranged as in the claims being rejected. Karsten Mfg. Corp. v. Cleveland Golf Co., and C.R. Bard, Inc. v. M3 Systems, Inc., supra. Under the authority of cases such as In re Arkley, 455 F.2d 586, 587-88 (CCPA 1972), it is impermissible to pick and choose among the hundreds of lines of text in a patent reference in order to arrive at the claimed subject matter. Okada, as stated above does not describe or exemplify any embodiment in which a concentration enhancing polymer required by Applicants is physically mixed with a solubility-improved form of a drug, again noting that a membrane surrounding a drug-containing core is not a "mixture".

To base an anticipation rejection on Okada one would need to select a particular polymer from among many polymers in Okada, home in on a particular drug in Okada, and then allege a physical mixture. But, Okada never discloses a physical mixture of one of Applicants' polymers and a solubility-improved drug form. The only disclosure in Okada of any polymer useful in Applicants' invention is in connection with making a membrane, not with mixing the polymer together with a solubility-improved drug in a physical mixture. The only disclosure of diclofenac sodium (noted by the Examiner in Paragraph 7 of the Office Action of 3/13/06) is in Example 9 where it is mixed with corn starch, not with a concentration-enhancing polymer. The hydroxypropyl cellulose also mentioned in Example 9 is not one of Applicants' required polymers, in addition to which Okada clearly applies it as a membrane, not in a physical mixture. To repeat, Okada does not disclose a physical mixture of a solubility-improved drug form and a concentration-enhancing polymer. To the extent Okada discloses any elements of Applicants' invention, they are disclosed in isolated and/or unrelated portions of the specification. A §102 rejection cannot be based on Okada by selecting out these isolated elements from the Okada specification and splicing them together, but with no direction in Okada to do so.

For all of the above reasons, it is requested that the anticipation rejection over Okada be withdrawn.

4. Claims 1, 30, 58, 86, 126 and 156-161 are not anticipated under 35 U.S.C. 102(e) by Bymaster et al. (US 6,147,072).

Bymaster discloses a method for treatment of psychoses in which a first component which is an atypical antipsychotic is administered in combination with a second component which is a serotonin reuptake inhibitor. Bymaster, column 1, lines 39-45. One of the dosage forms Bymaster discloses is an enteric formulation, created by coating a solid dosage form with a film of polymer, wherein the polymer can be the same as some of the polymers named by Applicants. Bymaster, column 10, lines 57-67.

The anticipation rejection over Bymaster should be withdrawn on the basis that Bymaster does not disclose a physical mixture of a solubility improved drug form and a concentration-enhancing polymer. The term "physical mixture" excludes Bymaster's embodiment in which the polymer is in a coating and the drug is incorporated into a core, the only embodiment of a drug and polymer disclosed in Bymaster. The arguments from above in respect of Okada are incorporated by reference, and it is noted that the Examiner framed substantially the same rejection in her final Office Action in respect of Bymaster as in respect of Okada. See paragraph 10 of the Office Action of March 13, 2006 in which the Examiner stated:

> Bymaster does describe chemical interaction between the drug and the polymer and the claims do not recite physical interaction or exclude chemical interaction.

Applicants again submit that the Examiner's interpretation is misplaced. Applicants' claims specifically require that the solubility improved drug form and the polymer are combined as a simple physical mixture, a term defined in the specification as discussed above. A physical mixture, having been defined as one in which the components are "mixed", recites physical interaction contrary to the Examiner's argument. Also, because the phrase "physical mixture" is defined as one in which the polymer and solubility-improved drug form retain their physical bulk properties, Applicants claims exclude chemical interaction.

The only occurrence in which a polymer required by Applicants' claims is coincidentally disclosed in Bymaster is as an enteric coating. Bymaster, column 10, lines 57-67. A dosage form in which an enteric polymer is coated around a core is not a physical mixture, however. Rather, it is a structure in which the membrane constitutes a fixed element. An act of physically

mixing is required to make a physical "mixture". That is the way Applicants defined the phrase "physical mixture", and Applicants' definition excludes a polymeric coating surrounding a drug-containing core because the polymer and drug are not physically mixed in such an embodiment. In Bymaster, no mixing of a polymer with a solubility-improved drug form is disclosed otherwise, nor any corresponding physical mixture.

Even in the section (column 10, lines 57-67) where Bymaster mentions some of Applicants' polymers for use as enteric coatings, the only specific disclosure of a drug is of duloxetine and of "duloxetine-containing combinations". Duloxetine per se is not a salt, however, much less a solubility-improved drug form. The Merck Index, Twelfth Edition, Published by Merck Research Laboratories, page 586, entry 3518, copy enclosed. In Bymaster's examples, there is no disclosure of any embodiment in which a solubility-improved drug form is physically mixed with a concentration-enhancing polymer required by Applicants' claims.

An anticipation rejection requires the presence in a single prior art reference of each and every element of the claimed invention, arranged as in the claims. Karsten Mfg. Corp. v. Cleveland Golf Co., and C.R. Bard, Inc. v. M3 Systems, Inc., supra. One cannot pick and choose from among unrelated portions of a disclosure to re-create a claimed invention. In re Arkley, supra. Applicants' position is that the Examiner has employed hindsight (i.e., the instant application) to choose a drug, choose a polymer, and then allege a physical mixture. But, such a physical mixture is nowhere disclosed in Bymaster. The anticipation rejection therefore has no legal basis and Applicants accordingly request that it be withdrawn.

5. Re claims 146, 147, 151-155, 162 and 163 being rejected as unpatentable under 35 U.S.C. 103(a) over Bymaster et al. (US 6,147,072).

It is noted that the above claims were rejected in Paragraph 9 of the Final Rejection of 3/13/06. For the sake of completeness, Applicants note that these claims have been canceled and that the rejection of these claims, as set forth in the Office Action, is accordingly moot.

6. Claims 87, 92, 95, 102, 105-107, 112, 115, 122, 124-127, 132, 135 and 142-145 are patentable under 35 U.S.C. 103(a) over Dunn (US 4,461,759).

It is well accepted that in order to establish a *prima facie* case of obviousness, an Examiner must satisfy three requirements: (1) there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art to modify

the reference or combine reference teachings; (2) the proposed modification of the prior art must have had a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the limitations of the claims. MPEP § 2142. In the instant rejection none of the three requirements has been satisfied - - (1) Dunn is completely silent about the problem of increasing the concentration of a low-solubility drug, (2) there is no "proposed modification" in Dunn that would lead one of ordinary skill to modify Dunn's teachings so as to physically mix a solubility-improved drug form and a concentration-enhancing polymer and (3) Dunn does not teach all elements, namely (a) a physical mixture of (b) a solubility-improved drug form with (c) a concentration-enhancing polymer thereby (d) enhancing drug concentration. Since Dunn lacks any suggestion or motivation to modify his teachings, there can be no reasonable expectation of success.

Applicants note that Dunn does disclose granulating, a form of physical mixing also disclosed in Applicants' specification. Dunn, column 4, lines 16-37. But Dunn does not disclose granulating a concentration-enhancing polymer with a solubility-improved drug form within the scope of Applicants' claims. The only drugs Dunn discloses within the scope of his claims are verapamil and verapamil hydrochloride, both of which are outside the scope of Applicants' claims, for reasons previously discussed - - neither species has "an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form". The language just quoted excludes the more soluble drug species whether it is the crystalline hydrochloride salt or the free base. The remaining form is also excluded by virtue of being the less soluble of the two forms.

Dunn cannot support an obviousness rejection because Dunn contains no teachings or suggestions relating to increasing the solubility of a poorly aqueous-soluble drug. Dunn is in fact concerned with the opposite problem to that solved by Applicants - - controlling the rate of dissolution for a drug that is highly or moderately water soluble. Dunn, column 1, lines 18-19. The Dunn formulations retard release rather than enhance concentration. Dunn, column 3, lines 41-63. It is untenable to conclude obviousness from Dunn considering that Dunn is unconcerned with the same technical problem as Applicants, is in fact concerned with the opposite problem, and achieves the opposite result.

Inasmuch as Dunn never discloses or suggests combining any solubility-improved drug form with a concentration-enhancing polymer, Dunn does not even disclose all the limitations of the claims. Accordingly, obviousness cannot lie. MPEP § 2142, supra.

Dunn also fails as an obviousness reference because verapamil hydrochloride, the only form of verapamil with which Dunn is concerned, is a highly soluble drug, well above the solubility limit of about 1 mg/mL imposed by Applicants. Dunn itself, in addition to stating that verapamil has a solubuility of 100 g/mL (column 2, bottom three lines), at column 1, lines 15-19, frames a problem stemming from a drug's high solubility when he states

> For such products, controlling their rate of solvation after ingestion also influences their rate of absorption, and drugs which are highly or moderately water-soluble present special formulation problems.

Although the solubility (100 g/mL) quoted in Dunn would seem to be an obvious misprint, the Examiner's attention is respectfully directed to The Merck Index, Twelfth Edition, Published by Merck Research Laboratories, Division of Merck & Co., Inc., Whitehouse Station, NJ, page 1696, entry 10083 (copy supplied herewith). The Merck Index cites verapamil hydrochloride as having a solubility in water of 83 mg/mL. That is a very high solubility, well above the "about 1 mg/mL" upper limit of solubility required by Applicants' claims. Clearly, given the context of Dunn and the specific problem framed therein, Dunn is unrelated to Applicants because verapamil hydrochloride has such a high aqueous solubility. Dunn simply does not suggest a physical mixture of a solubility-improved drug and a concentration enhancing polymer. Rather Dunn is concerned with a dosage form that is meant to dampen the high aqueous solubility of verapamil hydrochloride, which is outside the scope of solubility-improved forms allowed by Applicants. As such Dunn is unrelated to Applicants.

In conclusion, Appelicnts respectfully submit that the Examiner's final rejection of claims 1, 2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, 142-145 and 156-161 is without merit and should be withdrawn. Withdrawal of the patentability of the appealed claims is respectfully requested.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: March 13, 2007

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